

**REMARKS**

The Examiner has acknowledged Applicants' election of the invention of Group II (claims 24-53), as well as the species election of a drug (claim 27), a cytotoxic (claim 31), and a cellulose derivative (claim 35). However, the Examiner has summarily withdrawn claims 67-79, citing 37 C.F.R. 1.142(b). Applicants traverse the withdrawal of these claims as they were not unelected as required by 37 C.F.R. 1.142(b). Claims 67-79 depend from claim 27, and read on the elected species of a drug. Applicants respectfully request rejoinder of claims 67-79 with the pending claims. For the purposes of responding to the pending Office Action, Applicants assume that claims 24-27, 31, 35-53, and 67-80 constitute the pending claims currently under consideration in the present application. Applicants acknowledge that claims 28-30, 32-34, 62-66 and 81-96 are withdrawn from consideration as elected to a non-elected species. Applicants remind the Examiner that upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or which otherwise include all the limitations of an allowed generic species as provided in accordance with 37 C.F.R. 1.141. Applicants further submit that claim 24 is a generic linking claim.

Applicants have amended claims 24, 31, 35 and 80 merely to improve their form. Claim 24 has been amended to more particularly point out certain aspects of Applicants' invention. Specifically, claim 24 has been amended to recite a method of photokinetic transdermal delivery of a biologically active substance. Support for the claim amendment can be found throughout the specification and claims as filed. For example, support can be found in the abstract and at paragraphs 2, 11, 58, 71, 72 and 86 of the present specification. Claim 24 has also been amended to specify that the recited solution is applied to a cellular surface on the skin. Support for the claim amendment can be found throughout the specification and claims as filed. For example, support can be found in the abstract and at paragraphs 2, 12, 13, 60 and 62 of the present specification. In addition, claim 31 has been amended to more particularly point out certain aspects of Applicants' invention. Specifically, claim 31 has been amended to clarify that said cytotoxic is a cytotoxic drug. Support for the claim amendment can be found throughout the specification and claims as filed. For example, support can be found in originally filed claims 11 and 31 and at paragraphs 45 and 78 of the present specification.

Additionally, Applicants have added new claim 97. Support for the subject matter of the newly added claim can be found throughout the specification and claims as filed. Claim 97

corresponds to claim 27 as originally submitted. Applicants have also added new claim 98. Support for the subject matter of the newly added claim can be found throughout the specification and claims as filed. For example, support can be found in originally filed claims 23 and 41 and at paragraphs 55 and 85 of the present specification.

Applicants' amendments and newly added claims are fully supported by the specification. No new matter has been added. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

*Claim Rejections under 35 U.S.C. 112, second paragraph*

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action states that the phrase "comprises a cytotoxic" renders the rejected claim indefinite because it is unclear whether the limitation cytotoxic is a drug. Applicants respectfully traverse this rejection and contend that the rejection is moot in view of the amended claim.

The instant specification, at paragraph 45, states that "[e]xamples of drugs include, but are not limited to, ... cytotoxics." Therefore, it is clear and definite from the instant specification that a cytotoxic is a drug. Nevertheless, to expedite prosecution, Applicants have amended claim 31 to clarify the subject matter claimed. Specifically, Applicants have amended claim 31 to clarify that the claimed drug is a cytotoxic drug. Applicants' amendment is not in acquiescence to the rejection and does not narrow the scope of the claim. Reconsideration and withdrawal of this rejection are respectfully requested.

*Claim Rejections under 35 U.S.C. 102*

Claims 24-27, 31, 39 and 40 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Jiang *et al.* (Journal of Controlled Release, 19:41-58 (1992); hereinafter "Jiang"). Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants respectfully disagree with this rejection on the grounds that the Jiang reference does not disclose all of the elements of the rejected claims, particularly the claims as

amended. Applicants submit that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (see MPEP 2131).

First, as amended, claim 24, and dependent claims 25-27, 31, 39 and 40, are directed to photokinetic transdermal delivery of a biologically active substance by applying a solution comprising the biologically active substance to a cellular surface on the skin. Specifically, the instant method comprises applying the solution comprising the biologically active substance onto the surface of the skin. Pulsed incoherent light is then used to allow the biologically active substance to permeate the skin and enter the body of a subject without injection.

Jiang, however, has nothing to do with transdermal delivery of any agents. In fact, Jiang uses intravenous injection. Jiang relates to the use of photodynamic therapy, wherein photosensitizers are administered to patients by intravenous injection (see abstract and page 41, column 1, first paragraph to page 41, column 2, first paragraph). Applicants are unable to find where Jiang teaches transdermal delivery of a biologically active substance using pulsed incoherent light on the skin. In other words, Jiang relates to the use of photodynamic therapy to initiate a photochemical reaction inside a body, whereas the instant claims relate to a method for translocating a biologically active substance through the skin without injection. Jiang fails to teach the delivery of biologically active substances through the skin without injection.

Second, the rejected claims are directed to methods for transdermal delivery of a biologically active substance using pulsed incoherent light. As defined in the present specification at paragraph 65, pulsed incoherent light refers to "electromagnetic waves that are unorganized and propagate with different phases," and have "a discrete ON and OFF period."

Jiang fails to teach the use of "pulsed incoherent light." Specifically, Jiang relates to the use of photodynamic therapy, wherein photosensitizers are activated by light (especially laser light, which is coherent) to produce a cytotoxic chemical reaction (see abstract; page 41, column 1, first paragraph to page 41, column 2, first paragraph; and page 48, right column to page 49, left column). Applicants are unable to find where Jiang teaches the use of "pulsed" light (*i.e.*, light having discrete ON and OFF periods) as recited in the claims.

Thus, Jiang fails to disclose at least two elements of the claimed methods, and cannot anticipate the claimed invention.

Applicants' amendment is not in acquiescence to the rejection and is made solely to expedite prosecution. Applicants reserve the right to prosecute claims of similar or differing scope. The cited reference fails to teach or suggest each and every limitation of the claimed invention, and thus the cited reference fails to satisfy the criteria necessary for anticipating the claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

As Applicants note above in the section of the instant response discussing the status of the claims, Applicants contend that the Examiner has erroneously withdrawn claims 67-79, and that these claims are also presently under consideration. However, given that the Examiner temporarily withdrew claims 67-79 from consideration, the Examiner did not indicate whether or to what extent she would apply the instant rejection to any of these claims. Nevertheless, Applicants note for the record, that the foregoing arguments regarding the patentability of the claimed invention in view of Jiang apply at least equally to temporarily withdrawn claims 67-79. As such, all of the pending claims directed to the elected invention of Group II and the elected species are patentable over Jiang for, at least, the reasons outlined above. Given that Jiang fails to teach or suggest each and every limitation of the claimed invention, Jiang fails to satisfy the criteria necessary for anticipating the claimed invention.

#### Claim Rejections under 35 U.S.C. 103

Claims 24-27, 31, 35-53 and 80 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Jiang in view of Huang *et al.* (Journal of Photochemistry and Photobiology a: Chemistry, 108:229-233 (1997); hereinafter "Huang") and Kreindel *et al.* (U.S. Patent 6,387,089 B1; hereinafter "Kreindel"). Applicants respectfully traverse this rejection and contend that the rejection is moot in view of the amended claims.

Applicants contend that the cited references fail to satisfy the criteria necessary to render the claimed invention obvious. Nevertheless, to expedite prosecution, Applicants have amended claim 24 (and claims dependent thereon) to more particularly point out certain embodiments of Applicants' invention. Specifically, Applicants have amended the claims to more particularly point out that the methods of the invention relate to transdermal delivery of a biologically active substance. As amended, the claims are directed to photokinetic transdermal delivery of a biologically active substance by applying a solution comprising the biologically active substance to a cellular surface on the skin.

First of all, even assuming, for the sake of argument, that one of skill in the art is motivated to combine the cited art, the combined teaching still fails to teach or suggest all the claim limitations of the amended claims. As stated above, Jiang does not teach or suggest transdermal delivery of a biologically active substance using pulsed incoherent light on the skin. Huang and Kreindel fail to cure this deficiency because neither of these references teach or suggest transdermal delivery of a biologically active substance using pulsed incoherent light on the skin.

Specifically, Huang relates to the use of light to initiate a photochemical reaction that is cytotoxic to cultured cells, such as the U937 leukemia cells (see abstract; page 229, column 1, paragraph 1; and page 230, column 2, paragraph 2). There is no evidence that the light used in Huang is “pulsed.” The described methods are also irrelevant to transdermal drug delivery, since they are applied to test cells that are grown in tissue culture.

Although Huang mentioned in the last paragraph of the article that the method may be used to treat “superficial tumors” such as skin and oral cavity trachea, this does not amount to the teaching that the light can be used to enhance the penetration of biologically active substances through the skin (transdermal delivery). In fact, this arguably teaches away from transdermal delivery, because Huang also suggests in the same paragraph that “light ... cannot penetrate the human body deeply,” and one of skill in the art would have had read the whole paragraph to mean that the treatment method is limited to treating “superficial” disease conditions on the outer surface of the skin, and is not suitable to treat other diseases that require transdermal drug delivery – delivery of drug across the different skin layers and reach the underlying blood vessel (see paragraphs 0002 and 0062 of the instant specification).

Kreindel relates to the use of certain light, such as laser or pulsed incoherent light for heating and shrinking collagen within the skin (see abstract). However, the only use of the lights as disclosed in Kreindel is to heat the skin. In fact, there is no disclosure in Kreindel about any drug delivery at all, let alone transdermal drug delivery.

Therefore, none of the cited references (either individually or in combination) teaches or suggests a method of using pulsed incoherent light for transdermal drug delivery.

It naturally follows that one of skill in the art, in view of Jiang, Huang, and Kreindel, would have had no reasonable expectation of success to arrive at the claimed invention.

Applicants further submit that there is no motivation to combine the cited references as the Examiner suggested. The only reason provided in the Office Action to combine Jiang with

Kreindel is that Kriendel's pulsed incoherent light source "have the parameters suitable for implementing the invention such as light radiation [sic] should penetrate into a tissue in a millimeter depth; and applying a long pulse on a train of short pulses cools down the epidermis faster (as taught in Kriendel)." It is also unclear whether "cooling down the epidermis faster" imparts any advantage to the method in Jiang, which uses intravenous injection and has nothing to do with skin treatment or transdermal delivery. However, simply because prior art B teaches something (e.g., pulsed incoherent light source) that can be used in prior art A does not mean that there is a motivation to do so. Were that be the case, the Examiner can simply use Applicants' claimed invention as a roadmap and with the benefit of hindsight piece together any number of prior art references that happen to disclose the individual elements of the claimed invention, thereby totally obviating the need to provide a motivation to combine the references.

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.).

See MPEP 2143.01.

Therefore, all three requirements to establish a *prima facie* case of obviousness have not been met. Reconsideration and withdrawal of the obviousness rejection are respectfully requested.

As Applicants note above in the section of the instant response discussing the status of the claims, Applicants contend that the Examiner has erroneously withdrawn claims 67-79, and that these claims are also presently under consideration. However, given that the Examiner temporarily withdrew claims 67-79 from consideration, the Examiner did not indicate whether or to what extent he would apply the instant rejection to any of these claims. Nevertheless, Applicants note for the record, that the foregoing arguments regarding the patentability of the claimed invention in view of the combined teachings of Jiang, Huang and Kreindel apply at least equally to temporarily withdrawn claims 67-79. As such, all of the pending claims directed to the elected invention of Group II and the elected species are patentable over Jiang, Huang and Kreindel for, at least, the reasons outlined above. The combined teachings of Jiang, Huang and Kreindel fail to satisfy the criteria necessary to undermine the patentability of the claimed invention.

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000.

Applicants believe no fee other than those authorized in the Amendment Transmittal (filed concurrently herewith) is due in connection with the filing of this response. If, however, any other fee is due, please charge any deficiency in the fees that may be due (or credit any overpayment if appropriate) to **Deposit Account No. 18-1945**, from which the undersigned is authorized to draw, under **Order No. 002162-0001**.

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Respectfully submitted,

By \_\_\_\_\_

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